Remarks

Claims 1-2, 4-5, 8-12, 47-48, and 68-69 are pending upon entry of this Response. Claims 3, 6-7, 13-46, and 49-67 are canceled without prejudice or disclaimer. Claims 4-5, 11-12 and 47-48 are here amended, and new claim 69 is added.

Support for the amendment to claim 4 can be found at page 18, lines 21-24. Support for the amendment to claim 12 can be found in claim 4 as filed. Support for the amendment to claim 47 can be found at page 2, lines 16-17; and page 7, lines 3-12. Support for new claim 69 can be found at page 2, lines 16-17.

The pending specification is amended to remove references to deposits, as described below. A replacement sequence listing in compliance with 37 CFR §§ 1.821-1.825 is here submitted. No new matter is added.

Objections

Sequence listing

The Examiner on page 3, ¶ 7 objects to the sequence listing as failing to comply with the sequence rules set forth under 37 CFR §§ 1.821-1.825. The Examiner alleges that the amino acid sequence encoded by SEQ ID NO: 3 differs from the amino acid sequence set forth as SEQ ID NO: 2.

Applicants respectfully assert that the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 3 is identical to that in SEQ ID NO: 2 in the replacement sequence listing. In the event that an earlier substitute diskette has become defective, Applicants submit a replacement sequence listing in paper and computer readable form. Thus, this objection is moot, and Applicants respectfully request that the objection be withdrawn.

Specification

The Examiner on page 3, ¶¶ 8 and 9 objects to the specification as having omitted ATCC accession numbers and for the presence of improperly demarcated trademarks. In response, Applicants have amended the specification to delete references to the AS3 ATCC accession number, and to properly demarcate trademarks contained within the specification. Thus, this objection should be withdrawn.

Claims are directed to statutory matter under 35 U.S.C. § 101

Claim 11 is rejected on page 4, ¶ 11 under 35 U.S.C. § 101 as being directed to non-statutory subject matter, the Examiner stating that the broadest interpretation of the claim includes a transgenic human. Claim 11 as here amended is directed to "[a]n isolated host cell." Thus, claim 11 as amended excludes human beings, and is now directed to statutory subject matter. Applicants respectfully request that this rejection be withdrawn.

Claims 1, 2, 4-12, 47-49, 51 and 68 are rejected on page 4, ¶ 12 under 35 U.S.C. § 101 as being not supported by a specific and substantial asserted utility, a credible asserted utility, or a well-established utility.

Claims 6-7, 49 and 51 have been canceled, thus this rejection is moot in regard to these claims.

The requirements for satisfying the utility requirement are explained in the Manual of Patent Examination Practice (MPEP) 8th Edition, which states that only one credible assertion of specific and substantial utility, need be specified for an invention:

Specific Utility

> A "specific utility" is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. Office personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention. Assertions that fall in the former category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant. *Knapp v. Anderson*, 477 F.2d 588, 177 USPQ 688 (CCPA 1973).

Substantial Utility

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. Section 2107.01

Applicants traverse the rejection as applied to pending claims 1, 2, 4-5, 8-12, 47-48 and 68. Applicants submit that at least one substantial and specific utility was present in the application as filed for the claimed invention and is readily apparent based on the teachings of the specification. Claims as here amended are directed to nucleic acids of SEQ ID NOs: 1 and 3 and fragments thereof that are at least 250 nucleotides in length.

Applicants respectfully assert that the nucleic acids and polypeptides of the present claims have a specific, substantial, and credible utility, and therefore are patentable under 35 U.S.C. §101. The nucleic acids of SEQ ID NO: 1 and 3 encode prostate proliferation modulator AS3 and the AS3 polypeptide of SEQ ID NO: 2, which are useful, *inter alia*, for identification of cancer cells and for probing for cancer in prostate. Further, Applicants assert that the AS3 nucleic acid or protein are useful targets for therapeutic agents in such cancers. *See* specification at page 2, lines 15-17; and page 67, lines 1-14.

The application as filed is not a mere recitation of the nucleotide sequence of SEQ ID NO: 1, as it includes also data demonstrating a correlation with prostate proliferative conditions. Therefore the ordinarily skilled artisan reading the application at the time it was filed would have recognized that the compositions and methods described in the application are useful to distinguish prostate cancer from normal tissue. In contrast to a nucleotide sequence useful only to detect its complement, the nucleic acid of SEQ ID NO: 1 encodes protein AS3, which as shown by the specification as filed is inversely quantitatively related to normal phenotype in prostate cells, and is therefore a likely modulator of prostate cell proliferation.

For these reasons, Applicants assert that a substantial, specific, and credible utility was described in the specification, *viz*, that the nucleic acids of SEQ ID NOs: 1 and 3 and the

polypeptide of SEQ ID NO:2 can be used to distinguish prostate cancer from normal prostate tissue. Applicants respectfully request withdrawal of rejection of claims under 35 U.S.C. §101.

Claims satisfy 35 U.S.C. § 112 first paragraph

Claims are supported by substantial utility in the specification

Claims 1, 2, 4-12, 47-49, 51 and 68 are rejected on page 14, ¶ 14 under 35 USC §112, first paragraph, the Examiner asserting that the claimed invention is not supported by a specific and substantial asserted utility or a well-established utility.

Claims 6-7, 49 and 51 have been canceled, thus this rejection is moot in regard to these claims. Applicants have explained above the patentable utility of the claimed invention. For the same reasons, Applicants also submit they have taught how to use the claimed invention.

Claimed are enabled by the specification

Claims 1, 2, 4-12, 47-49, 51 and 68 are rejected for lack of enablement, the Examiner stating that the nucleotide sequence of SEQ ID NO: 1 is different from the nucleotide sequence disclosed in GENBANK Accession No. U95825 ("U95825"). Claims 6-7, 49 and 51 have been canceled. Thus, this rejection is moot in regard to these claims.

The Examiner on page 15 of the Office Action admits that the nucleotide sequence of SEQ ID NO: 1 differs from the nucleotide sequence of U95825 at 20 bases. As this sequence has a length of 5,271 nucleotides, these nucleotide sequences are in fact 99.6% identical. This percent identity is within the limits of polymorphisms of a gene as found within a population.

Further, the amino acid sequence of SEQ ID NO: 2, which is 1,391 amino acids in length and is encoded by the nucleic acids of SEQ ID NOs 1 and 3, differs from the amino acid sequence of U95825 at 14 residues out of a total of 1391 residues. Thus, these amino acid sequences are 99.0% identical, i.e., at the amino acid sequence level, the proteins are merely two polymorphisms, i.e., naturally occurring variants of the same gene.

The specification as filed provides AS3 and its polymorphisms, which are described as having small numbers of changes in the amino acid sequence of the AS3 protein provided. *See*, page 18, lines 9-14 of the specification. Therefore, the specification as filed enables one of skill in the art to use the provided AS3 nucleic acids and polypeptides, and thereby to recognize and obtain such polymorphisms. Because the extent of identity of the two amino acid sequence is

within the level of that of polymorphisms, Applicants assert that claims 1, 2, 4-5, 8-12, 47-48, and 68 are fully enabled.

The Examiner further states that the amino acid sequence of SEQ ID NO: 3 encoded by the open reading frame of SEQ ID NO: 1, differs from the amino acid sequence set forth in SEQ ID NO: 2. Because electronic errors can be introduced with passage of time, Applicants submit herewith a replacement sequence listing in paper and computer readable form. Applicants assert that the amino acid sequence encoded by SEQ ID NO: 3 as originally submitted and as identically resubmitted here is identical to the amino acid sequence set forth as SEQ ID NO: 2 in the replacement sequence listing.

Claims 4-12 are rejected for lack of enablement in the Office Action at pages 15-16, ¶16. The Examiner asserts that the specification does not reasonably provide enablement for an isolated nucleic acid molecule which encodes a naturally occurring allelic variant of the polypeptide sequence of SEQ ID NO: 2; an isolated nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence at least about 70% identical to the amino acid sequence of SEQ ID NO: 2; and an isolated nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid comprising the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3. Claims 6 and 7 have been canceled. Thus, this rejection is moot in regard to these claims.

Claim 4 as here amended is directed to an isolated nucleic acid molecule that encodes a naturally occurring allelic variant of a polypeptide having the amino acid sequence set forth in SEQ ID NO:2, encoding a polypeptide having a function of the polypeptide of SEQ ID NO: 2, the allelic variant having "...a conservative substitution of an amino acid of SEQ ID NO:2...". The specification as filed provides allelic variants of the AS3 polypeptide, at. page 18, lines 9-24. Further, the specification at page 19, lines 10-14, provides nucleic acid molecules from different species encoding an AS3 polypeptide. Murine AS3 polypeptide having GENBANK accession numbers AY102267 and NM_175310 (denoted androgen-induced proliferation inhibitor (ARPIN)), is highly homologous to its human counterpart SEQ ID NO: 2, as shown in the attached Appendix A. The present claims do not, contrary to the assertions on p. 17 of the Office Action, encompass all possible mutated forms of the sequences at each position. Further, the specification as filed provides examples of allelic variants with a small percent of conservative substitutions. Therefore claim 4 as here amended is enabled by the specification.

Claim 5 as amended is directed to an isolated nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1 or 3, or a complement thereof. Such fragments are provided by the application at page 60, lines 2-7, and claim 5 as originally filed. Therefore Applicants assert that claim 5 as here amended is enabled by the specification as filed.

Claims 8-12 depend directly or indirectly from claims 1, 2, 4 and 5, therefore claims 8-12 incorporate the amendments herein to these claims.

In rejecting Claim 10, the Examiner admits on page 21, ¶ 17 of the Office Action that the specification is "...enabling for making and using an isolated host cell...". Applicants here amend claim 10 which is now directed to an isolated host cell. Claim 10 as amended does not pertain to a transgenic animal or human nor to a non-human animal. Thus, this rejection is overcome.

Claims 47 and 51 are rejected on page 24, ¶ 18 for lack of enablement. Claim 51 has been canceled, thus this rejection is moot with respect to claim 51.

With respect to claim 47, the Examiner on , page 25 of the Office Action states that the claims encompass a kit for use in diagnosing a broad genus of diseases involving altered cell proliferation. The Examiner further states that "... the threshold level of expression that delineates a prostate cancer cell from a normal prostate cell has not been disclosed...".

Claim 47 as here amended is directed to a kit for diagnosing a prostate cell proliferation condition or an increased likelihood of developing prostate proliferative disorder, compared to an unaffected mammal. Further, claim 47 has been amended to depend from claim 5, therefore incorporates limitation of this claim to the nucleotide sequence of a fragment of at least 250 nucleotides of SEQ ID NOs:1 or 3.

Applicants assert that methods and data showing different levels of AS3 in proliferating prostate cells compared to non-proliferating cells (such as non-cancerous cells of the prostate) are disclosed by the specification as filed, and that the use of these assays would not require an undue amount of experimentation. The specification discloses at page 74, lines 27-29, that non-proliferative, i.e., normal prostate cells express between 3-4 and 5-6 fold higher levels of AS3 mRNAs than proliferative prostate cells.

Therefore, the specification as filed provided ranges of expression of the AS3 nucleic acid, with which one of ordinary skill in the art could distinguish a prostate cell having a

proliferative condition from a normal prostate cell. Thus, claim 47 as here amended is enabled by the specification as filed. Applicants respectfully request that this rejection be withdrawn.

Written Description

On page 14, ¶14 of the Office Action, claims 4-12 are rejected under 35 U.S.C 112 ¶ 1, the Examiner stating that the nucleotide sequence of SEQ ID NO: 1 is different from the nucleotide sequence disclosed in GENBANK Accession No. U95825. Claims 6-7 have been canceled, thus this rejection is moot as applied to these claims.

Nucleotide sequences are discussed in the previous section. As shown above, claim 4 as here amended here is directed to an isolated nucleic acid molecule that encodes a naturally occurring allelic variant comprising a conservative substitution of an amino acid, of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2, the polypeptide having a function of the polypeptide of SEQ ID NO: 2.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g.*, Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. The specification as filed provides that a conservative amino acid substitution includes one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Further, the specification at page 19, lines 10-14, provides that AS3 nucleotides are identified based on the nucleotide sequence of human AS3 (e.g., SEQ ID NO: 1 or SEQ ID NO: 3).

As shown in attached Appendix A, several conservative amino acid substitutions are apparent from comparing mouse and human AS3 polypeptides. For example, amino acids at positions 1325-1327 in SEQ ID NO:2 (human AS3) are glutamic acid, and are conservatively replaced with three aspartic acid residues at positions 1323-1325 in murine AS3. *See* Appendix A. Thus, one of ordinary skill in the art would recognize that Applicants were in possession of the nucleic acid and the nucleotide sequence of claim 4, as here amended, at the time the application was filed.

Claim 5 as here amended is directed to an isolated nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1 or 3, or a complement thereof. Thus, one of ordinary skill in the art would recognize all

members of the genus of fragments encompassed by claim 5, as here amended. Therefore, claim 5 as amended satisfies the written description requirement.

Claims 8-12 depend directly or indirectly from claims 1, 2, 4 and 5 and incorporate amendments to claims from which they depend. Since claims 1, 2, 4, and 5 as here amended satisfy the written description description, claims 8-12 also satisfy this requirement. Applicants respectfully request that these rejections be withdrawn.

Claims as amended satisfy 35 U.S.C. § 112 second paragraph

Claims 47 and 51 are rejected on page 30, ¶ 21 as being indefinite. Claim 51 has been canceled., thus this rejection is moot with respect to claim 51.

The Examiner states that claim 47 is indefinite as including the phrase "a disease involving altered cell proliferation" Applicants here amend claim 47 to delete this phrase. The Examiner further rejects claim 47 as indefinite in reciting "an increased likelihood." As here amended, claim 47 is directed to "a kit for diagnosing a mammal for the presence of a prostate cell proliferative condition or an increased likelihood of developing a prostate cell proliferative condition compared to an unaffected mammal."

Applicants assert that claim 47 as here amended is definite, and request that this rejection be withdrawn.

Claims are novel

Geck et al., J. Steroid Biochem. and Mol. Biol. 68:41-50, 1999

Claims 5-12, 47 and 51 are rejected on page 32, ¶ 23 as anticipated by Geck et al., J. Steroid Biochem. and Mol. Biol. 68:41-50, 1999. Claims 6-7 and 51 have been canceled, thus this rejection is moot with respect to these claims.

Applicants traverse this rejection to the extent it applies to claims 5, 8-12, and 47 as here amended, for the following reasons. Applicants here submit a Declaration under 37 CFR § 1.132 by Prof. Ana Soto, an inventor of the present invention.

Prof. Soto and Peter Geck, Jozsef Szelei, and Carlos Sonnenschein are co-authors of the 1999 Geck publication and are co-inventors of the present application. Prof. Soto states that

Jesus Jimenez, a co-author of the 1999 Geck paper, worked under her direction and supervision and was not a co-inventor of the subject matter claimed in the present patent application.

As Jimenez was not a co-inventor, the 1999 Geck paper is not an invention by another inventive entity, i.e., the inventive entity of the authors of the paper is the same as the inventive entity of the present application. Applicants respectfully request that this rejection be withdrawn.

Geck et al., J. Steroid Biochem. and Mol. Biol. 63:211-18, 1997

Claims 5-7, 9-11, 47 and 51 are rejected on page 32-33, ¶ 24, as anticipated by Geck et al., J. Steroid Biochem. and Mol. Biol. 63:211-18, 1997. Claims 6-7 and 51 have been canceled. Thus this rejection is moot with respect to these claims.

Applicants traverse this rejection as it applies to claims 5, 9-11, and 47 as here amended, for the following reasons. Claims 5-7, 9-11, and 47 as here amended are directed to isolated nucleic acid molecules having sequences of SEQ ID NO:1 or SEQ ID NO: 3, as well as fragments of these sequences greater than 250 nucleotides in length, and vectors, isolated host cells, and kits containing these nucleic acids.

The standard of rejection for anticipation is identity. The 1997 Geck publication at Table 1 (page 214) indicates that a 262 base pair fragment of AS3 is 98% identical to a nucleic acid deposited as Genbank accession number U50533. However, the 1997 Geck publication does not disclose any nucleic acid or amino acid sequences, much less the specific sequences of any of the isolated nucleic acids of SEQ ID NO:1 or SEQ ID NO: 3, or fragments thereof. The Examiner states that the nucleic acid molecule of the prior art is deemed the same as the claimed nucleic acid molecule. However the 262 base pair fragment of the prior art, with no disclosed nucleic acid sequence, does not describe the sequence of the entire molecule. Therefore, pending claims 5-7, 9-11, and 47, as here amended, are not anticipated by the 1997 Geck publication.

The Examiner asserts on p. 33 of the Office Action that "...the polynucleotide sequence of the molecule is an inherent property of the molecule."

The standard of rejection for inherency is predictability for each and every occurrence. Mere possession of a portion of a sequence does not anticipate the entire sequence. The genome is rife with cryptic genes and non-functional pseudo-genes. Further, genes contain introns that are differently processed at different tissues and stages of development. Possession of a small

portion of a sequence is merely a tool to explore the myriad of homologous sequences, and is not possession of an intact isolated nucleic acid.

Further, the 1997 Geck publication indicates that there are at least two mRNA species to which the 262 base pair AS3 fragment hybridizes, an 8.0kb and a 5.5kb variant. (See, e.g., Figures 4-7). Geck et al. 1997 fail to provide a sequence for either of these variants, and fail to disclose which of these encodes AS3. Thus, the required predictability for each and every occurrence is clearly absent from the 1997 Geck publication. Applicants respectfully request that these rejections be withdrawn.

Promega 1993/1994 Biological Research Products Catalog

Claim 47 is rejected on page 34, ¶ 26 as anticipated by Promega 1993/1994 Biological Research Products Catalog. The Examiner states that Promega "discloses a kit comprising a material for measuring RNA; although the catalog does not expressly disclose that the material can be used to measure RNA encoding AS3, the product of the prior art is deemed the same as the product of the claims." (Office Action at page 35).

Applicants point out that claim 47 as amended is directed to a kit that comprises the nucleic acid of claim 5 *viz.*, a fragment of at least 250 nucleotides of a nucleic acid having the nucleotide sequence of SEQ ID NO:1 or 3, or a complement thereof.

The standard for rejection for anticipation is identity. Since the Promega catalog does not disclose any of the nucleotide sequences of SEQ ID NO:1 or 3, or a complement thereof, Promega does not anticipate present claim 47. Applicants respectfully request that this rejections be withdrawn.

Boehringer Mannheim 1994 catalog Biochemicals

Claim 51 is rejected as anticipated by Boehringer Mannheim 1994 catalog, Biochemicals. Claim 51 has been canceled. Thus, this rejection is moot in regard to this claim.

Applicants respectfully request that rejections of claims under 35 U.S.C. § 102 be withdrawn.

Claims are non-obvious

Geck et al., J. Steroid Biochem. and Mol. Biol. 68:41-50, 1999

Claims 5-12, 47 and 51 are rejected on page 35, ¶ 26 of the Office Action as obvious in view of the 1999 Geck publication. Claims 6-7 and 51 have been canceled, thus this rejection is moot as regards these claims.

Applicants traverse this rejection with respect to claims 5, 8-12, and 47 as here amended, for the following reasons.

As stated above, Applicants submit here a Declaration under 37 CFR § 1.132 by Dr. Ana Soto, an inventor of the present invention, stating that she and Peter Geck, Jozsef Szelei, and Carlos Sonnenschein, co-authors of the 1999 Geck publication, are proper co-inventors of the application, and that Jesus Jimenez, the other co-author is properly not named as an inventor in the present application. Jimenez worked under her direction and supervision. As 1999 Geck et al. is not an invention by another, the present invention is not obvious in view of this art. Therefore Applicants respectfully request that this rejection be withdrawn.

Bendig et al., Genetic Engineering 7:91-127, 1988

Claim 48 is rejected on page 36, ¶ 30 as obvious in view of the 1999 Geck et al. publication in view of Bendig et al., Genetic Engineering 7:91-127, 1988.

Applicants point out that claim 48 as here amended is directed in part to "(a) providing a cell with DNA encoding the AS3 (Androgen Shutoff Gene 3) polypeptide of SEQ ID NO: 2, the DNA being positioned for expression in the cell."

As shown above, Geck et al. 1999 is not the work of another and is therefore not prior art. As it is not prior art under 35 U.S.C. 102, it cannot be used as the basis for rejection of the present claims under 35 U.S.C. 103.

Bendig et al. is merely a review article describing expression of foreign proteins in mammalian cells. Bendig does not disclose or suggest any AS3 polypeptide; thus it does not remedy the deficiencies of Geck et al. 1999

As neither Geck et al. 1999 nor Bendig, alone or in combination, render the present claims obvious, this rejection has been overcome and should be withdrawn.

GENBANK Accession No. U95825, in view of Knappik et al., Biotechniques 17:754-61, 1994

Claims 5-12, 47, 48 and 51 are rejected as anticipated by the 1997 Geck publication, as evidenced by GENBANK Accession No. U95825, in view of Knappik et al., Biotechniques 17:754-61, 1994. Claims 6-7 and 51 have been canceled and this rejection is moot for these claims.

Applicants traverse this rejection as applied to claims 5, 8-12, 47 and 48, for the following reasons. The present application claims the benefit of U.S. provisional Application No. 60/121,461, filed on February 24, 1999.

A GENBANK revision history of the sequences of AS3, available at: http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi?val=U95825, for Accession No. U95825 shows that this sequence first appeared at GENBANK on March 30, 1999 as GI4539617. This entry was later replaced by GI4559409 (also under the U95825 Accession number) on April 15, 1999.

Neither of these dates of deposit of sequences into GENBANK antedate the claimed priority date.

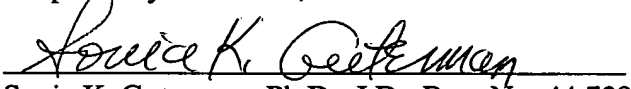
Further, Knappik shows production of a fusion protein comprising a polypeptide of interest and a heterologous polypeptide such as FLAG, and does not teach or suggest any AS3 nucleic acid or polypeptide sequence.

For either of these reasons, neither Knappik nor the 1997 Geck publication and GENBANK, alone or in combination, render the present claims obvious. Thus, this rejection of claim 5, 8-12, 47 and 48 should be withdrawn.

Conclusion

Based on the present amendments and remarks, Applicants submit that the present claims are in condition for allowance, and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is invited and encouraged to contact Applicants' attorney or agent at the telephone number below.

Respectfully submitted,



Sonia K. Guterman, Ph.D., J.D., Reg. No. 44,729
Gregory Sieczkiewicz, Ph.D., Reg. No. 48,223
Attorney/Agent for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer no. 30623

Dated: May 17, 2004